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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
BOWMAN, AMY HUDSON	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 11/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/824,036	MCSWIGGEN, JAMES	
	Examiner	Art Unit	
	Amy H. Bowman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 April 2005 and 14 October 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/22/04, 7/19, 8/11 05*
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 18 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is unclear where the sentence ends because claim 18 does not end with a period. Appropriate correction is required.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The invention of the above claims is drawn to a chemically synthesized double stranded siNA molecule that directs cleavage of a HD RNA via RNA interference, wherein each strand of said siNA molecule is about 19 to about 23 nucleotides in length, to various modifications of the siNA molecule, and to a pharmaceutical composition comprising the siNA molecule.

At the outset, it is noted that the claims do not recite a specific target nucleotide sequence by SEQ ID NO, but rather refer to the broad genus of HD sequences.

The claims encompass chemically synthesized double stranded siNA molecules that direct cleavage of any HD RNA via RNA interference, as well as encompass those that target any HD homolog or allele known or yet to be discovered from any species of HD, as well as DNA genomic fragments, splice variants or polynucleotide fragments that express proteins that retain HD -like activity.

Although the specification discloses specific siNA sequences having complementarity to a HD sequence, the specification does not describe siNA molecules directed to any other species of HD polynucleotides to describe the instantly claimed genus of siNA molecules directed to any HD gene. Each of the instantly disclosed siNA molecules is targeted to a single sequence, although the claims are drawn to any HD sequence. It is the structure of each specific siNA molecule that leads to its function with regards to a specific target sequence. One of ordinary skill in the art could not make such oligos to any HD without knowledge of the sequence. Given the breadth of sequences embraced in the instantly claimed genus, one could not envision the member oligonucleotides that target such a broad genus and one would not recognize that applicant was in possession of the claimed genus at the time the invention was made.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).
In the instant case, the effective filing date of the instant claims is determined to be that of the application 10/783,128, which has an effective filing date of 2/20/2004. The instant case 10/824,036 does not receive the benefit of any of the earlier filed priority documents because none of the documents disclose siNA molecules that direct cleavage of the instantly recited target, HD. Thus, the instant claims are accorded an effective filing date of 2/20/2004.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-9, 13-15, and 18-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hayden et al. (US 2002/0187931 A1), in view of Davidson et al. (US 2004/0241854 A1), Tuschl et al. (WO 02/44321), Elbashir et al. (The EMBO Journal, Vol. 20, No. 23, pages 6877-6888, 2001), Parrish et al. (Molecular Cell, Vol. 6, pages 1077-1087, 2000) and Morrissey et al. (US 2003/0206887).

The invention of the above claims is drawn to a chemically synthesized double stranded double stranded siNA molecule that directs cleavage of a HD RNA via RNA interference, wherein each strand of said siNA molecule is about 19 to about 23 nucleotides in length, and at least one strand comprises one or more chemically modified nucleotides. The invention is further drawn to various modifications to the siNA molecule, as well as a pharmaceutical composition comprising the siNA molecule.

Hayden et al. teach that antisense oligonucleotides can target the cellular gene or mRNA transcribed from that gene that encodes the huntingtin protein. Hayden et al. teach that the antisense oligonucleotide can be modified to exhibit desirable properties such as, for example, enhanced cellular uptake, enhanced affinity for the nucleic acid target, and increased stability in the presence of nucleases (see page 7). Hayden et al. teach that the antisense oligonucleotides comprise from about 15 to about 30 nucleotides. Hayden et al. teach pharmaceutical compositions comprising the oligonucleotide antagonist and a pharmaceutically acceptable.

Hayden et al. do not teach siRNA duplexes that cleave HD RNA via RNA interference. Hayden et al. do not teach the specific modifications instantly recited.

Davidson et al. teach siRNA duplexes specific for the huntingtin gene. Davidson et al. is relied upon as further evidence that siRNA duplexes are appropriate means of inhibiting huntingtin target gene expression. Even without the Davidson et al. reference, the invention of the above claims is obvious in view of the antisense inhibition of huntingtin taught by Hayden et al.

Tuschl et al. teach siRNA duplexes consisting of two separate RNA strands, wherein each strand is 19-25 nucleotides, preferably 21 nucleotides (see pages 3 and 7). The duplexes are capable of mediating RNAi (see page 3). One strand of the duplex is preferably 100% complementary to the target (see page 6). Tuschl et al. disclose that the dsRNA of their invention can be 21 nucleotide siRNA duplexes with 3' overhangs or with blunt ends wherein the two strands are fully complementary to each other and one strand is fully complementary to at least part of a transcript of a target gene (see page 44, line 25, and figure 11). Tuschl et al. teach that the 5'-terminus preferably comprises a phosphate group (see page 4). The most effective dsRNAs are composed of two 21 nt strands which are paired such that 1-3, preferably 2 nt 3' overhangs are present on both ends of the dsRNA. Tuschl et al. teach chemical modifications at the 5' and/or the 3/ end of the dsRNA molecule (see page 5) for stabilization against degradation. Tuschl et al. teach 2'-deoxy, 2'-O sugar modifications and phosphorothioates. Tuschl et al. teach pharmaceutical compositions comprising the siRNA and a carrier or diluent. Tuschl et al. teach that siRNAs represent a new alternative to antisense or ribozyme therapeutics.

Elbashir et al. teach chemically modified 21-nucleotide siRNA duplexes that mediate RNA interference. Elbashir et al. teach duplexes that are 100% modified, which are considered to comprise no ribonucleotides. Elbashir et al. teach 2'-deoxy or 2'-O-methyl modification to various locations of the duplex and teach that different modifications are well tolerated in different areas of the duplex.

Parrish et al. teach modified double stranded siRNA molecules comprising a first nucleotide sequence with complementarity to a target and a second nucleotide sequence with complementarity to said first nucleotide sequence, wherein one or both of the nucleotide sequences are modified and at least 19 nucleotides are complementary between the first and second sequences. The siRNA molecules are an antisense/sense pair of oligomers. Parrish et al. teach 2'-deoxy-2'-fluoro pyrimidine modifications in the sense or antisense strand (see figure 5).

Morrissey et al. teach terminal glyceryl modification to siNA constructs to preserve RNAi activity in cells and dramatically increase the serum stability of the compound (see page 6).

It would have been obvious to one of ordinary skill in the art specifically target an siRNA to a HD gene, since Hayden et al. teach antisense inhibition of HD and Tuschl et al. teach that siRNAs are new alternatives to antisense oligonucleotides. Antisense oligonucleotides and siRNA duplexes are both sequence specific inhibitors of target gene expression. Additionally, Davidson et al. specifically teach siRNA duplexes targeted to HD, which further evidences that siRNA duplexes are appropriate means to target and inhibit the expression of a HD gene.

Furthermore, it would have been obvious to one of ordinary skill at the time the invention was made to incorporate 2'-deoxy-2'-fluoro modifications, as taught by Parrish et al.; to incorporate phosphorothioates, 2'-O-methyl nucleotides, or 2'-deoxy nucleotides, as taught by Tuschl et al.; or to incorporate a glyceryl moiety, as taught by Morrissey et al. One would have been motivated to incorporate each of these modifications since each of these modifications were known in the art to add beneficial properties to oligonucleotides, such as increasing nuclease resistance and stability of the duplex. Hayden et al. teach that antisense oligonucleotides can be modified to exhibit desirable properties such as enhanced cellular uptake, enhanced affinity for the nucleic acid target, and increased stability in the presence of nucleases. These are the same benefits taught in the siRNA art for modifying siRNA duplexes. One would have been motivated to gain such benefits for siRNAs as well as antisense oligonucleotides, as each are sequence specific inhibitors of target gene expression. One would have been motivated to place such modifications in various locations of the siRNA duplex, as Elbashir et al. teaches such testing of siRNA duplexes to optimize the performance.

Finally, one would have a reasonable expectation of success given that Elbashir et al. and Tuschl et al. each teach designing siNA molecules to direct cleavage of known genes and the HD gene was known to be previously targeted by modified antisense oligonucleotides, as demonstrated by Hayden et al. Elbashir et al. and Tuschl et al. each teach a method of synthesizing siRNA duplexes that are complementary to a pre-selected target. Additionally, each of the modifications instantly claimed were known in the art to add benefits to antisense oligonucleotides or siRNA

duplexes, each of which one would reasonably expect to benefit an siNA targeted to HD.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Claims 1, 6, 10-12, 16 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hayden et al. (US 2002/0187931 A1), in view of Tuschl et al. (WO 02/44321) as applied in the 35 U.S.C. 103(a) rejection above, and further in view of Matulic-Adamic et al. (U.S. 5,998,203).

The teachings of Hayden et al. and Tuschl et al. are relied upon for reasons explained in the 35 U.S.C. 103(a) rejection above, to establish obviousness of targeting a modified siRNA duplex to a huntingtin RNA. These pieces of art do not teach polynucleotide or non-nucleotide linker molecules and do not teach terminal cap moieties.

The invention of the above claims is drawn to a chemically synthesized double stranded double stranded siNA molecule that directs cleavage of a HD RNA via RNA interference, wherein each strand of said siNA molecule is about 19 to about 23 nucleotides in length, and at least one strand comprises one or more chemically modified nucleotides. The invention is further drawn to polynucleotide or non-nucleotide linker molecules, as well as terminal cap moieties.

Matulic-Adamic et al. teach double stranded short interfering nucleic acid molecules that comprise a first nucleotide sequence complementary to a target or a portion thereof, and a second sequence having complementarity to said first sequence. Matulic-Adamic et al. teach chemical modifications of the double stranded structure. Such enzymatic RNA molecules are taught to be targeted to virtually any RNA transcript and achieve efficient cleavage (see column 1) and to be sufficiently complementary to a target sequence to allow cleavage. Matulic-Adamic et al. teach the incorporation of chemical modifications at the 5' and/or 3' ends of the nucleic acids to protect the enzymatic nucleic acids from exonuclease degradation, which improves the overall effectiveness of the nucleic acid, as well as facilitates uptake of the nucleic acid molecules (see column 2). Matulic-Adamic et al. teach base, sugar and/or phosphate modification, as well as terminal cap moieties at the 5'-cap, 3'-cap, or both. Specifically, 3' phosphorothioates, inverted abasic moieties, and 2'-O-methyl modifications are utilized. Matulic-Adamic et al. teach 2'deoxy nucleotides and 2'-deoxy-2'-halogen nucleotides, wherein Br, CL and F are representative halogens (see column 3, for example).

It would have been obvious to one of ordinary skill in the art to incorporate polynucleotide or non-nucleotide linkers, as well as terminal cap moieties such as inverted abasic moieties, as taught by Matulic-Adamic et al. into a siRNA duplex targeted to a HD gene. One would have been motivated to incorporate each of these modifications since each of these modifications were known to add benefits such as protecting the enzymatic nucleic acids from exonuclease degradation, as taught by

Matulic-Adamic et al. Hayden et al. teach that antisense oligonucleotides can be modified to exhibit desirable properties such as enhanced cellular uptake, enhanced affinity for the nucleic acid target, and increased stability in the presence of nucleases. These are the same benefits taught in the ribozyme and siRNA art, as taught by Matulic-Adamic et al. and Tuschl et al., respectively. One would have been motivated to gain such benefits for siRNAs as well as antisense oligonucleotides or ribozymes, as each are sequence specific inhibitors of target gene expression. Additionally, Tuschl et al. teach that siRNA duplexes represent a new alternative to antisense or ribozyme therapeutics.

Finally, one would have a reasonable expectation of success given that Tuschl et al. each teaches designing siNA molecules to direct cleavage of known genes and the HD gene was known to be previously targeted by modified antisense oligonucleotides, as demonstrated by Hayden et al. Additionally, Matulic-Adamic et al. teach that the enzymatic RNA molecules can be targeted to virtually any RNA transcript and achieve efficient cleavage (see column 1). Each of the modifications were known in the art to benefit ribozymes, as taught by Matulic-Adamic et al. Therefore, one would reasonably expect the same benefits to a siNA molecule.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 1-31 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-31 of copending Application No. 10/783,128. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented. Claims 1-31 of the instant application are identical to claims 1-31 of copending application 10/783,128.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy H. Bowman whose telephone number is 571-272-0755.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now

contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see http://pair-direct.uspto.gov.

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Amy H. Bowman
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PATENT EXAMINER